MANAGEMENT OF ADRENOCORTICAL INSUFFICIENCY DURING SURGERY

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This is the article in the November, 1955 ARCHIVES OF SURGERY, in which J. F. K. 's surgeon, Dr. James A. Nicholas, describes his preparations for an "ADDISONIAN CRISIS" in an unnamed 37-year-old man who underwent spinal surgery at Manhattan's Hospital for Special Surgery on October 21, 1954 - the same day and the same hospital where 37-year-old John F. Kennedy underwent the same operation.

Management of Adrenocortical Insufficiency During Surgery

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Adrenocortical insufficiency, known to be present in patients with Addison's disease and in patients who have had bilateral adrenalectomy, may also be induced in patients who have been receiving therapy with cortisone or other corticosteroids. The possibility of death following surgical intervention in such persons has been pointed out.* This is particularly apt to occur in cases where emergencies require surgery to be performed without benefit of prior work-up and preparation.

We wish to describe our experiences in the management of three patients with adrenocortical insufficiency, each with a different problem, who required surgical intervention. We have had six patients with hypoadrenalism at the Hospital for Special Surgery in the past two years who required surgery; hence, it is by no means a rare problem. Five of the six patients had cortisone-induced cases of hypoadrenalism. All were prepared for surgery but one, and in only one who required emergency surgery did death occur. The data on three of these patients are being presented in this paper to illustrate the methods whereby we managed the problems.

One patient had been receiving intensive hydrocortisone therapy for rheumatoid arthritis when he developed acute appendicitis. A second patient had suppressed adrenocortical function produced by cortisone therapy for pemphigus, and he required an elective femoral replacement arthroplasty of the hip. A third patient had known Addison's disease and needed spinal and sacroiliac fusions. Each of these patients presented different problems in the management of their adrenocortical deficiency. The successful results obtained in all but one case were due mainly to the extended metabolic work-up prior to, during, and after surgery. The scale of trauma in the surgery of these cases is very intense.

REPORT OF CASES

Case 1.—*Example of Hydrocortisone-Induced Adrenocortical Insufficiency Requiring Emergency Surgery*

A man 47 years of age entered the clinic for rheumatic diseases of the Hospital for Special Surgery in 1940 because of rheumatoid arthritis involving the neck, shoulders, wrists, and knees. Gold therapy was started but was discontinued because it produced severe dermatitis. On Aug. 14, 1949, he was given 25 mg. of corticotropin (ACTH) by intramuscular injection, which resulted in good relief of his pains with diminution of his stiffness. Therefore, he was started on corticotropin therapy of 50 mg. twice a day. In January. 1950, his treatment was changed to desoxycorticosterone acetate (DCA) in 5 mg. doses on alternate days, combined with ascorbic acid. In November, 1951, his treatment was changed to hydrocortisone with phenylbutazone. This was maintained thereafter on low dosage. Despite this, he gained weight and developed some facial edema at times.

On Nov. 7, 1954, the patient was brought to the hospital in acute distress due to appendicitis. Ap-

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* References 1, 2, 3, and 4.

pendectomy with drainage of a retrocecal abscess was performed during cyclopropane anesthesia. Preoperatively he was given an infusion of 1000 cc. of 5% dextrose in water. During the operation, intravenous therapy was continued with 250 cc. saline and 500 cc. of blood because the patient's hemoglobin was 11.4 gm. per 100 cc. of blood. All other vital signs were within normal limits. During the operation his arterial blood pressure, pulse rate, and respiratory rate remained normal. But immediately postoperatively, as he was emerging from anesthesia, severe surgical shock developed, characterized by low arterial blood pressure, rapid thready pulse, and cold clammy skin. The intravenous administration of 100 mg. of hydrocortisone free alcohol in 1000 cc. of 5% dextrose in saline resulted in considerable improvement within a half hour. Nine days later, viscera broke through the wound. Closure was made with through-and-through nonabsorbable surgical (silk) sutures during cyclopropane anesthesia, at which time an intravenous infusion of 1000 cc. of 5% dextrose in saline containing 100 mg. of hydrocortisone was administered. Immediately postoperatively he again manifested severe surgical shock, and he was treated with good results by the intravenous administration of another 100 mg. of hydrocortisone. Four days later a fecal fistula developed. The patient died a week later, after an episode of pyrexia which was not affected by antibiotic therapy. Autopsy revealed massive septicemia, with abscesses scattered throughout the peritoneum, the peribronchial tissue, and the myocardium. The adrenals were atrophic. One adrenal gland weighed 3.2 gm., the other 2 gm., with marked thinning of the cortex.

This case illustrates that prolonged therapy with hydrocortisone can result in hypocorticalism and that when such a patient requires surgical intervention, even of a relatively minor nature, he may require supplemental hydrocortisone to treat a crisis of acute adrenocortical insufficiency. Hypocorticalism was demonstrated both anatomically and functionally: anatomically, by the atrophy of both adrenal glands, with thinning of the cortex, and, functionally, by the states of surgical shock which developed following each of two relatively minor surgical procedures. In each instance, this complication occurred as soon as anesthesia wore off. In the first instance blood tranfusion which was considered greater in quantity than the amount of blood lost during the appendectomy was ineffectual in preventing the postanesthetic shock. In both instances the hypotensive state was corrected by the intravenous administration of additional hydrocortisone.

This case illustrates two other important points. First, patients receiving corticosteroid therapy may develop susceptibility to certain infections poorly responsive to antibiotics. Second, the administration of general anesthesia to such patients undergoing surgery may block or delay the state of acute adrenal cortex insufficiency until the effects of anesthesia are dissipated.

This case was the only fatality in our series, and death occurred not from hypocorticalism but from the massive sepsis, which may have been enhanced by our treatment of his insufficiency.

CASE 2.—*Example of Elective Surgery in a Patient with Cortisone-Induced Hypocorticism*

A lawyer 43 years of age had been treated for pemphigus with cortisone for 5 years. His daily dose of cortisone had ranged from 200 to 1000 mg. Complications which ensued included cortisone-induced psychosis, which was treated by electroshock therapy, cortisone-induced osteoporosis, and bilateral avascular necrosis of the femoral heads together with avascular necrosis of the left humeral head. The patient developed so much pain and stiffness in his legs that he sought help and agreed to a prosthetic replacement of his left femoral head, which was performed on Jan. 13, 1954.

Preoperative laboratory findings disclosed that this patient had certain stigmata of hypoadrenalism. These included a failure to retain water, with high urinary output and arterial hypotension. When given 50 mg. of corticotropin in a 4-hour infusion, he did not retain salt nor did his 17-ketosteroid excretion rise. His total eosinophile count did not drop after this test. It was clear that this patient needed salt and adequate cortisone therapy, the dosage of which was to be determined by daily metabolic studies. He was given 2 liters of isotonic saline intravenously the first 24 postoperative hours and cortisone intramuscularly every 4 hours in doses of 50 to 100 mg. at a time, so that his daily dosage ranged between 400 and 600 mg. for 3 days. After the third day, results of the patient's blood chemistry studies were within normal limits and his urinary output and salt loss were normal. The first 2 days were characterized by wide swings in blood pressure and salt excretion. Twenty-four and 12 hours preoperatively he was given 100 mg. of cortisone intramuscularly.

On the day of operation the patient was given preanesthetic medication consisting of procainamide hydrochloride, 500 mg. orally, 75 minutes before anesthesia, and morphine sulphate, 10 mg., combined with scopolamine hydrobromide, 0.4 mg., injected hypodermically one hour before anesthesia. The intramuscular administration of cortisone was maintained. Anesthesia was induced by the intravenous injection of 400 mg. of hexobarbital sodium (Evipal Sodium) in a 2% aqueous concentration. This was followed by the administration of cyclopropane-oxygen anesthesia. During the operation, fluid therapy consisted of saline (1000 cc.), 6% dextran (500 cc.), blood (500 cc.), and 5% dextrose in water (500 cc.).

The patient was managed with saline and cortisone alone, and he was brought through the planned surgical procedure successfully. However, he required constant attention because he had nine bouts of hypotension in the first 72 hours. Salt excretion during this time was high, being 300 mEq. for the first 24 hours postoperatively.

We do not advocate this method for coping with the problem, but it is interesting to note that, despite the loss of a check rein on salt loss, patients requiring large-scale surgery can successfully survive.

CASE 3.—*Example of a Patient with Adrenal Insufficiency Due to Addison's Disease Requiring Elective Surgery* †

A man 37 years of age had Addison's disease for seven years. He had been managed fairly successfully for several years on a program of desoxycorticosterone acetate pellets of 150 mg. implanted every three months and cortisone in doses of 25 mg. daily orally. Owing to a back injury, he had a great deal of pain which interfered with his daily routine. Orthopedic consultation suggested that he might be helped by a lumbosacral fusion together with a sacroiliac fusion. Because of the severe degree of trauma involved in these operations and because of the patient's adrenocortical insufficiency due to Addison's disease, it was deemed dangerous to proceed with these operations. However, since this young man would become incapacitated without surgical intervention, it was decided, reluctantly, to perform the operations by doing the two different procedures at different times if necessary and by having a team versed in endocrinology and surgical physiology help in the management of this patient before, during, and after the operation.

It was planned to manage this patient with hydrocortisone intravenously throughout the surgical period and postoperatively as needed, supplementing this with desoxycorticosterone, saline, and cortisone as indicated. At 24 and 12 hours preoperatively he was given 100 mg. of cortisone intramuscularly.

The operation was accomplished on Oct. 21, 1954. Preanesthetic medication consisted of an opium preparation (Pantopon), 10 mg., and atropine sulphate, 0.4 mg., injected hypodermically one hour before induction of anesthesia. Anesthesia was obtained by the intravenous injection of 300 mg. of hexobarbital sodium in a 2% aqueous concentration followed by cyclopropane with oxygen. Endotracheal intubation was performed with a cuffed No. 36 Magill tube, and the patient was turned onto the prone position. Preanesthetic arterial blood pressure was 100 mm. Hg systolic and 64 mm. diastolic. The pulse rate was 72 per minute. These circulatory levels were maintained remarkably stable throughout the entire operation, which lasted more than 3 hours. The electrocardioscope which was observed during the procedure showed a regular sinus rhythm at all times. Fluid therapy consisted of 2000 cc. of blood to compensate for a similar amount of blood loss produced by the lumbosacral fusion followed by the sacroiliac fusion (both were done, since the patient's condition remained good). In addition, the patient received 100 mg. of hydrocortisone in 1000 cc. of 5% dextrose in saline, which was administered intravenously during the surgical procedure.

The postoperative course was satisfactory in that no Addisonian crisis developed at any time during the next 2 months. The urinary salt excretion during this time varied between 5 and 10 gm. a day, necessitating some replacement, and the arterial blood pressure was maintained within normal limits. To prevent negative salt balance, adequate amounts of desoxycorticosterone and saline were periodically administered. Minor complications, consisting of a urinary tract infection on the third postoperative day, a transfusion reaction characterized by mild angioneurotic edema, and a mild wound infection despite antibiotic therapy, occurred. In each instance increased cortisone and salt were given. Four months later, the patient was subjected to another surgical intervention for the removal of a Wilson plate which had been used in the spinal fusion as a form of fixation. The same program of management as used in the previous operation was employed, except that anesthesia was provided by means of local infiltration with 1% hexylcaine (Cyclaine) solution together with thiopental sodium by intravenous drip merely sufficient to cause drowsiness. No sequelae were noted other than the need for increased cortisone and added amounts of salt and desoxycorticosterone immediately postoperatively. Water retention was never a problem.

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† Dr. Ephraim Shorr, of the New York Hospital, provided advice in the management of this case.

This case is noteworthy because desoxycorticosterone provided a check rein on the tendency to develop salt loss and arterial hypotension. Desoxycorticosterone, it will be recalled, is an adrenocortical-like steroid that permits reabsorption of salt in the kidneys so that urinary salt loss is minimized. Though this patient had marked adrenocortical insufficiency, though the magnitude of his surgery was great, and though complications ensued postoperatively, this patient had a smooth postoperative course insofar as no Addisonian crisis ever developed.

ANESTHESIOLOGICAL CONSIDERATIONS

As to the effect of anesthesia on adrenocortical function during surgical trauma, previous studies have shown that uncomplicated general anesthesia modifies the usual response of the adrenal cortex to surgical stress.‡ By using the eosinophile count as an index of adrenocortical activity, it has been shown that the stress of surgical trauma produces a marked fall in the eosinophile count in the circulating blood.§ With use of this eosinopenic response with a fall of more than 50% of the eosinophiles as a criterion, it was observed that eosinopenia did not occur in 83% of the patients during uncomplicated general anesthesia for operations lasting more than 2 hours but that it did appear when the anesthesia wore off.[6] Similar studies during uncomplicated spinal anesthesia with surgery were less conclusive, in that 40% of the patients showed an eosinopenic response both during spinal anesthesia with surgery and after spinal anesthesia had worn off.[6] Although eosinophile counts in themselves provide only a rough estimate unless carefully done, they, along with urinary salt excretion, are useful aids in the day-to-day management of these patients.

Since acute adrenocortical insufficiency is accompanied by impaired homeostatic adjustments to stress, with inability to compensate for various circulatory disorders, it is important to avert stress-imposing reactions. Thus, high spinal anesthesia or deep general anesthesia, both of which may cause arterial hypotension, should be avoided. Sympathetic blockade produced by drugs such as pentamethonium, hexamethonium, or trimethaphan camphorsulfonate (*d*-3,4[1′,3′-dibenzyl-2′-ketoimidozolido]-1,2-trimethylene thiophanium *d*-camphor sufonate) (Arfonad) should also be avoided, since pharmacological sympathetic blockade so produced may result in marked arterial hypotension from which recovery might be difficult. Respiratory depression from any cause should be prevented at all times. An excitement stage during induction of anesthesia should be averted by proper preanesthetic medication and by use of a small dose of an intravenous barbiturate. The management of postoperative pain should aim at securing pain relief without causing respiratory or circulatory depression.

COMMENT

The endocrinological and metabolic management of patients with hypocorticalism who require elective surgical therapy is important. It is suggested that such patients be made research projects for a biochemical team wherever feasible, in order to determine their metabolic status.

The preoperative estimation of hypocorticalism depends upon various factors. In the case of known Addison's disease, the diagnosis is obvious. Induced hypocorticalism resulting from prolonged therapy with cortisone or other corticosteroids should be suspected in any patient receiving such therapy prior to surgical intervention. Patients who have been treated with cortisone for only one or two weeks may, rarely, have suppressed adrenocortical function. In such cases corticosteroid therapy should be continued if surgery is required. If the patient has been receiving his treatment by oral administration, therapy should be maintained parenterally when the oral route is discontinued on the day of operation. There is an analogy here to diabetic patients requiring insulin therapy: in both instances endocrine therapy must be maintained, increased as necessary, but never interrupted. Although we have not seen prednisone (Meticorten)-

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‡ References 5 and 6.

§ References 7, 8, and 9.

induced insufficiency, we presume that it, too, will be shown to occur.

When time permits, certain laboratory determinations are useful in planning individual management before, during and after surgery. Biochemical tests that are important include the eosinophile counts and electrolyte excretion in response to intravenous corticotropin; estimation of the 17-ketosteroids, the 17-hydroxycorticoids, and the acid steroid fraction[11] in the urine; measurement of daily urinary output; estimation of daily urinary salt excretion; determination of blood levels of sodium, potassium, chloride, and CO_2-combining power, and water load tests.

The following suggestions are advocated in the management of patients with hypocorticalism who require surgical intervention and anesthesia, although each case requires individualized treatment.

1. Increase the amount of corticosteroid preoperatively if the patient has been receiving such therapy. Never cease or decrease it unless it is possible to postpone surgery until a normal adrenal response has been reestablished.

2. Increase the salt intake during and after surgery. If salt loss is occurring, 6 to 9 gm. of sodium chloride may be necessary for the total daily replacement.

3. Estimate blood loss and fluid loss accurately and administer these amounts to the patient. Ascertain whether the patient is sweating and provide for appropriate salt replacement.

4. Be prepared to treat arterial hypotension that is not due to blood loss by the intravenous administration of hydrocortisone. This should be given by placing 100 mg. in a liter of saline and administering this quantity in from one to four hours.

5. Watch for signs of fluid retention by palpating the patient's bony prominences.

6. If increased stress, such as a postoperative infection, occurs, increase the amount of salt intake and of cortisone if necessary. However, decrease the cortisone thereafter as rapidly as possible. It may be advisable to change to desoxycorticosterone to diminish salt loss in excessive quantity rather than rely on high cortisone administration.

7. As soon as a salt balance can be obtained and maintained by oral intake, the dosage of corticosteroid should be diminished gradually but as rapidly as possible.

8. To maintain good nutrition, large amounts of protein are indicated. Sometimes it may be advisable to enhance this effect by the administration of testosterone.

9. These patients should be watched carefully day and night from the time of surgery until a proper metabolic and electrolyte balance is obtained. Asthenia, lassitude, weakness, and arterial hypotension indicate impending adrenocortical crisis. A low CO_2-combining power, excessive urinary salt loss, and low serum chloride and sodium also should alert one to the need for treatment. Hypokalemia must also be guarded against when using these steroids even as replacement.

10. In case of salt retention (as evidenced by edema) the amount of salt intake should be diminished. Desoxycorticosterone should be discontinued if it is being given then, but hydrocortisone or cortisone should be made available. If necessary, it may be wise to provide some potassium if too much sodium retention is present.

11. The urinary output should be measured and charted. Daily urinary output of more than 2000 cc. postoperatively the first 3 days should be suspected of containing an excess of salt loss, unless as a result of high fluid intake. Water intoxication and salt-losing nephritis should be ruled out.

12. If the patient has some cardiac disease with diminished cardiac reserve, other therapeutic aids should be given as indicated and the salt load must be watched carefully.

SUMMARY AND CONCLUSIONS

The management of three patients with adrenocortical insufficiency, each with a different set of conditions and each requiring surgery, is described. One patient had hypocorticalism induced by prolonged hydrocortisone therapy for rheumatoid arthritis; he survived two emergency operations but finally succumbed to septicemia. A second patient had cortisone-induced hypocorticalism and required a rather large-scale elective operation. The third patient was a known Addisonian who required an elective spinal fusion and sacroiliac fusion. All three patients were protected from the development of an adrenal crisis, though each of the patients was managed in a different manner. All required cortisone or hydrocortisone postoperatively in increased amounts. The management will vary, however, from patient to patient, depending upon many factors.

Some anesthesiological considerations on this problem are given. In the main these include avoidance of stress-imposing reactions, such as arterial hypotension and respiratory depression.

Patients who need surgical intervention and who have depressed adrenocortical function as a result of therapy with some corticosteroid may be managed safely through surgery of rather severe degree. If the proposed surgical procedure is of an elective nature, the optimum method of management would be to postpone the time of surgery until corticosteroid therapy has been discontinued and a sufficient length of time has elapsed to allow demonstration of normal adrenal reserve. If corticosteroid therapy must be continued, then it should not be discontinued during the time of surgical management; rather, corticosteroid therapy should be increased preoperatively, whether the surgical problem is an emergency or not. In the case of an elective procedure under such circumstances, the management is similar to that of the patient with known Addison's disease. The preoperative period should be utilized to evaluate the patient's metabolic and electrolyte requirements. Increased cortisone 24 hours before surgery is advised. During surgery, hydrocortisone should be given intravenously and sufficient salt intake should be given to the patient at all times. Postoperatively, corticosteroid therapy should be maintained as required by the patient in the immediate convalescent period, but it should be reduced gradually as rapidly as possible to prevent the possibility of sepsis and infection. Desoxycorticosterone is a very valuable salt-saving adjunct and should be used if necessary.

It is important to bear in mind that adrenocortical insufficiency may persist for many weeks after prolonged corticosteroid therapy has been discontinued. The adrenocortical response of patients who require surgical intervention should be investigated carefully in order to avert acute adrenocortical insufficiency.

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